

## A Patient with IgA Monoclonal Gammopathy Presenting as Myelomatous Pleural Effusion with Axillary Node Involvement

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Multiple myeloma is a cancer of plasma cells that produce monoclonal immunoglobulin, and the neoplastic plasma cells typically accumulate in the bone marrow with occasional involvement of other organs. Pleural effusion that is associated with multiple myeloma has been infrequently reported (<6%) and myelomatous pleural effusion is extremely rare (<1%). A 73-year-old woman was admitted to the department of dermatology for skin lesions on both arms and both ankles. A chest radiograph taken on admission showed a nodular lesion in the right upper lung and pleural effusion. Analysis of the pleural fluid revealed many atypical plasma cells, elevated levels of IgA (27.95g/L) and lambda light chain (9.16g/L), and monoclonal IgA-lambda paraprotein on immunofixation. The serum concentrations of IgA were elevated (33.08g/L) while the concentrations of IgG and IgM were decreased. Bone marrow aspirate smears contained increased levels of immature-appearing atypical plasma cells. This is only the third case of myelomatous pleural effusion that has been reported in Korea. (*Korean J Hematol* 2006;41:41-45.)

**Key Words:** Multiple myeloma, Pleural effusion, IgA-lambda paraprotein

### INTRODUCTION

Multiple myeloma (MM) is a disease in which neoplastic plasma cells accumulate in the bone marrow and generally produce a monoclonal immunoglobulin, usually of type IgG or IgA.<sup>1)</sup> Malignant plasma cells may also affect other organs. Although the involvement of rib and sternum is relatively common, associated pulmonary parenchymal or pleural disease has been reported infrequently.<sup>2,3)</sup> Pleural effusion in MM has been

reported in less than 6% of cases and myelomatous pleural effusion (MPE) is extremely rare (<1%).<sup>4,5)</sup> MPE is most commonly associated with IgA or IgG myeloma and very rarely with IgD or light chain myeloma.<sup>6-9)</sup> Only two cases of MPE associated with MM have been reported in Korea to date: one with IgG-kappa and the other with IgD-lambda myeloma.<sup>3,9)</sup> The present study involves a patient with IgA-lambda MM who presented with skin lesions and pleural effusion.

접수 : 2006년 1월 30일, 수정 : 2006년 2월 17일

승인 : 2006년 2월 22일

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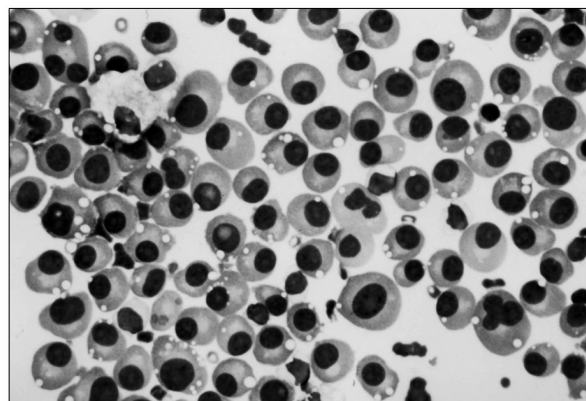
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# CASE REPORT

A 73-year-old woman was admitted to the dermatology department for skin lesions on both of her arms and ankles. She had been followed up in the dermatology department for 7 months for evaluation of erythematous macules and papules on her arm. Her symptoms persisted and the lesions spread to the lower extremities. No remarkable findings were seen on physical examination other than edematous ankles with tenderness of the newly developed lesions.

Chest radiography revealed the persistence of a previously noted nodular lesion in the upper right lung and a newly developed blunting of the right costophrenic angle (CPA) suggestive of pleural effusion. Upon admission, her hemoglobin concentration was 106g/L (10.6g/dL; reference interval, 120~160g/L [12.0~16.0g/dL]), white cell count  $4.86 \times 10^9/L$  ( $4,860/\mu L$ ; reference interval,  $4.0 \sim 10.8 \times 10^9/L$  [ $4,000 \sim 10,800/\mu L$ ]), and platelet count  $270 \times 10^9/L$  ( $270 \times 10^3/\mu L$ ; reference interval,  $150 \sim 400 \times 10^9/L$  [ $150 \sim 400 \times 10^3/\mu L$ ]). Serum creatinine, calcium, total protein, and albumin levels were  $70.7 \mu\text{mol/L}$  ( $0.8\text{mg/dL}$ ; reference interval,  $44.2 \sim 123.76 \mu\text{mol/L}$  [ $0.5 \sim 1.4\text{mg/dL}$ ]),  $2.3\text{mmol/L}$  ( $9.3\text{mg/dL}$ ; reference interval,  $2.2 \sim 2.7\text{mmol/L}$  [ $8.7 \sim 10.8\text{mg/dL}$ ]),  $84\text{g/L}$  ( $8.4\text{g/dL}$ ; reference interval,  $58 \sim 78\text{g/L}$  [ $5.8 \sim 7.8\text{g/dL}$ ]), and  $30\text{g/L}$  ( $3.0\text{g/dL}$ ; reference interval,  $34 \sim 53\text{g/L}$  [ $3.4 \sim 5.3\text{g/dL}$ ]), respectively. Laboratory tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), and cryoglobulins were negative.

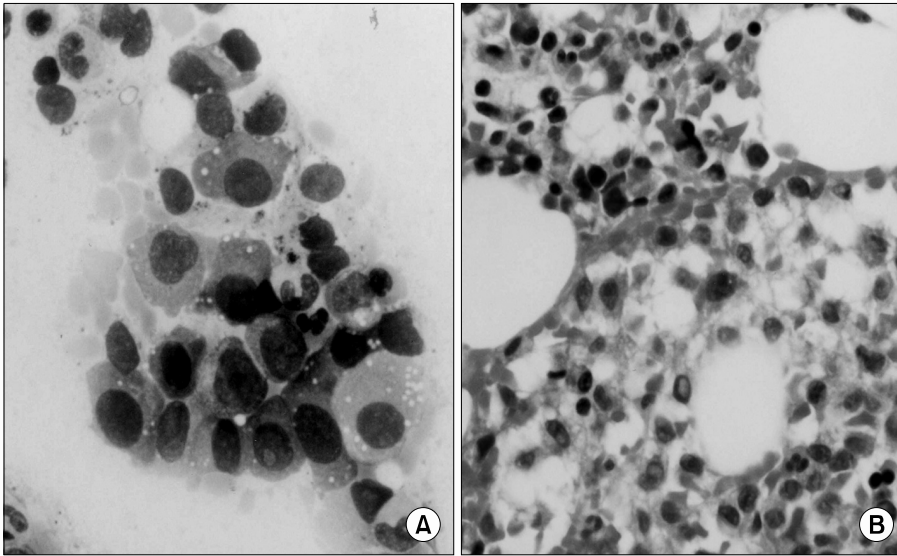
Thoracentesis was performed due to persistent pleural effusion, and the cytospin smears of the pleural fluid revealed clusters of atypical plasma cells, suggestive of plasmacytoma or multiple myeloma (Fig. 1). Quantitation of immunoglobulin and light chain in the pleural fluid showed increased concentrations of IgA ( $27.95\text{g/L}$ ,  $2,795\text{mg/dL}$ ) and lambda light chain ( $9.16\text{g/L}$ ,  $916$



**Fig. 1.** Cytospin smears of pleural fluid showing clusters of plasma cells with marked atypia such as anisocytosis, immature forms, and multinucleation (Wright-Giemsa,  $\times 1,000$ ).

mg/dL). Serum protein electrophoresis revealed a monoclonal peak in the beta and gamma globulin region, with markedly elevated serum IgA ( $33.08\text{g/L}$  [ $3,308\text{mg/dL}$ ]; reference interval,  $1.0 \sim 4.9\text{g/L}$  [ $100 \sim 490\text{mg/dL}$ ]) and lambda light chain ( $10.1\text{g/L}$  [ $1,010\text{mg/dL}$ ]; reference interval,  $0.9 \sim 2.1\text{g/L}$  [ $90 \sim 210\text{mg/dL}$ ]) and decreased levels of IgM ( $0.34\text{g/L}$  [ $34\text{mg/dL}$ ]; reference interval,  $0.5 \sim 3.2\text{g/L}$  [ $50 \sim 320\text{mg/dL}$ ]), IgG ( $5.41\text{g/L}$  [ $541\text{mg/dL}$ ]; reference interval,  $8.0 \sim 17.0\text{g/L}$  [ $800 \sim 1,700\text{mg/dL}$ ]), and kappa light chain ( $1.46\text{g/L}$  [ $146\text{mg/dL}$ ]; reference interval,  $1.7 \sim 3.7\text{g/L}$  [ $170 \sim 370\text{mg/dL}$ ]). Immunofixation confirmed the monoclonal IgA-lambda chain peak. Immunofixation of the pleural fluid was consistent with that of serum, demonstrating the presence of a monoclonal IgA-lambda paraprotein. A bone marrow study was performed in which the bone marrow aspirate smears exhibited increased levels of plasma cells, with marked atypia such as anisocytosis, immature forms, and double nuclei involving 51% of all nucleated cells, thus substantiating the diagnosis of multiple myeloma (Fig. 2).

A punch biopsy of the leg on the second hospital day revealed leukocytoclastic vasculitis (LCV) with multiple fibrin thrombi. On the seventh day, the patient complained of swelling of the right



**Fig. 2.** Bone marrow aspiration and biopsy. (A) Aspiration smear showing increased atypical plasma cells with immature forms. (B) Biopsy section showing infiltration of immature plasma cells (A: Wright-Giemsa,  $\times 1,000$ ; B: Hematoxylin and Eosin (H&E),  $\times 400$ ).

arm and a soft and fixed mass was incidentally found on the frontal scalp area. Punch biopsy of the scalp lesion showed mild superficial perivenular lymphocytic infiltration. A breast ultrasonogram was performed to determine the cause of edema, indicating multiple lymph node enlargement of the right axilla and a huge multiseptated mass at the right supraclavicular area, suggestive of a possible malignant lymphoma, metastatic malignant lesion, or tuberculosis. A fine needle aspiration biopsy of the axillary lymph node showed diffuse infiltration of mature and immature plasma cells, consistent with plasma cell myeloma. The right supraclavicular mass appeared malignant, with possible pathologic diagnoses of extraosseous plasmacytoma with metastasis, malignant lymphoma, inflammatory reactive lymphadenopathy or metastatic malignancy involving lymph nodes from lung, breast, or stomach cancer. The follow up was lost because the patient was transferred to another hospital for further treatment.

## DISCUSSION

We report a case of late stage MM with associated malignant pleural effusion, leukocytoclastic vasculitis and lymphedema. The most

common cause of the MM-related pleural effusion is congestive heart failure, due to either amyloidosis or atherosclerotic heart disease. Other less common causes include pulmonary embolism, chronic renal failure, a second neoplasm, and myelomatous pleural involvement.<sup>10)</sup> Malignant pleural effusion in MM is extremely rare, occurring in less than 1% of patients.<sup>4)</sup> In Korea, only two cases of myeloma with associated MPE have been reported to date, one IgG-kappa and one IgD-lambda,<sup>3,9)</sup> and its prevalence has not been reported. In the present study, myelomatous effusion was diagnosed by detection of IgA-lambda type monoclonal immunoglobulin and atypical plasma cells in the pleural fluid. It should be noted that protein electrophoresis of pleural fluid may be unreliable since hemorrhagic effusions are common, and pleural biopsy may show a low diagnostic yield of plasma cell infiltrates due to frequent non-uniform pleural involvement.<sup>11)</sup> The differential diagnoses based on the morphology of plasma cells in pleural effusion include MM, lymphoma with plasmacytic differentiation, and metastatic non-hematolymphoid neoplasia such as melanoma and neuroendocrine carcinoma. IgA gammopathy is more frequently represented in MM cases with MPE,<sup>12)</sup> implying a difference in propensity to

develop MPE according to the type of paraprotein. Pleural effusion is indicative of a dismal prognosis in MM and generally represents a late complication of progressive and disseminated disease.<sup>10-12)</sup> Patients with MPE usually respond poorly to available therapy and the mortality rate reaches 90% within 1 year. In a recent report of 11 patients who developed MPE approximately 12 months after being diagnosed with MM, the median survival was 4 months from the onset of MPE, suggesting that MPE in MM is often associated with a poor prognosis despite aggressive local and systemic treatment.<sup>12)</sup>

LCV is an inflammatory necrotizing disease of the superficial dermal vessels that is associated with a variety of diseases including infections, drug reactions, connective tissue disorders, ANCA-associated vasculitides, as well as malignancies involving both solid tumors and lymphoproliferative disorders.<sup>13)</sup> Since LCV has been observed in association with so many disease states, it has been difficult to clarify the relationship between LCV and malignancies. However, the cutaneous manifestation of the patient in this study may have been associated with late stage MM, since she did not have any apparent connective tissue disorders or ANCA-associated vasculitides. Cytokine release by tumor cells, which induces an immunologic reaction against vascular smooth muscle cells, is one of several pathogenic mechanisms that have been proposed to explain this connection.<sup>14)</sup> It has also been suggested that patients with a poorer prognosis or with late stage MM may be predisposed towards the development of LCV due to an increased immunologic response.<sup>14)</sup>

In conclusion, recognition of the malignant nature of the pleural effusion is of great importance for therapeutic and prognostic considerations and can be achieved by cytological examination, immunoelectrophoresis, and flow cytometric analysis of the pleural fluid. Likewise, a screening

examination to detect any underlying neoplasms may be warranted in elderly patients with apparently idiopathic cutaneous LCV and clinical symptoms suggestive of malignancy.

## 요 약

다발성골수종은 형질세포의 악성종양으로 주로 골과 골수를 침범하여 골파괴, 골수부전, 고칼슘혈증, 신부전, 빈번한 감염과 이상단백인 M-component 면역글로불린을 분비하는 질환이다. 다발성골수종은 신체의 거의 모든 장기와 조직에 골수종세포가 침투할 수 있으며, 그 중 가장 흔히 동반되는 장기는 간, 비장, 림프절, 신장 등이 있다. 다발성골수종에서 골수종세포의 늑막 침범에 의한 늑막삼출 동반 예는 보고가 적다. 저자들은 다발성골수종의 주변 림프절과 늑막 침범에 의해 늑막삼출이 동반된 1예를 진단하고 이를 문헌고찰과 함께 보고하는 바이다.

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